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INTERNATIONALE ANMELDUNG VERÖFFENTLICHT NACH DEM VERTRAG ÜBER DIE  
INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT)

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(54) Title: PROPHYLAXIS AND THERAPY OF CORONARY HEART DISEASES BY LOWERING THE ESTRO-  
GEN CONCENTRATION

(54) Bezeichnung: PROPHYLAXE UND THERAPIE VON KORONAREN HERZKRANKHEITEN DURCH SEN-  
KUNG DES ÖSTROGENSPIEGELS

(57) Abstract

Utilisation of antiestrogen and aromatase inhibitors, optionally in combination with  $\beta$ -receptor blockers for the prophylaxis and therapy of coronary heart diseases. Substances such as tamoxifen are considered to be used as antiestrogen, and such as testolactone to be used as aromatase inhibitors.

(57) Zusammenfassung

Verwendung von Antiöstrogenen und Aromatasehemmern, gegebenenfalls in Kombination mit  $\beta$ -Rezeptorenblockern, zur Prophylaxe und Therapie von koronaren Herzkrankheiten. Als Antiöstrogenen kommen Substanzen wie Tamoxifen und als Aromatasehemmer solche wie Testolacton infrage.

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<p>(21) Internationales Aktenzeichen: PCT/DE84/00137</p> <p>(22) Internationales Anmeldedatum: 19. Juni 1984 (19.06.84)</p> <p>(31) Prioritätsaktenzeichen: P 33 23 321.7</p> <p>(32) Prioritätsdatum: 24. Juni 1983 (24.06.83)</p> <p>(33) Prioritätsland: DE</p> <p>(71) Anmelder (für alle Bestimmungsstaaten ausser US): SCHERING AKTIENGESELLSCHAFT (DE/DE); Berlin und Bergkamen, Müllerstrasse 170/178, D-1000 Berlin 65 (DE).</p> <p>(72) Erfinder;und (75) Erfinder/Anmelder (nur für US) : SCHULZE, Paul, Eberhard (DE/DE); Endestrasse 30, D-1000 Berlin 39 (DE). KERB, Ulrich (DE/DE); Prinzregentenstrasse 7, D-1000 Berlin 31 (DE).</p>	<p>(81) Bestimmungsstaaten: DE (europäisches Patent), FR (europäisches Patent), GB (europäisches Patent), JP, NL (europäisches Patent), US.</p> <p>Veröffentlicht <i>Mit internationalem Recherchenbericht.</i></p>	
<p>(54) Title: PROPHYLAXIS AND THERAPY OF CORONARY HEART DISEASES BY LOWERING THE ESTRO- GEN CONCENTRATION</p> <p>(54) Bezeichnung: PROPHYLAXE UND THERAPIE VON KORONAREN HERZKRANKHEITEN DURCH SEN- KUNG DES ÖSTROGENSPIEGELS</p> <p>(57) Abstract</p> <p>Utilisation of antiestrogen and aromatase inhibitors, optionally in combination with <math>\beta</math>-receptor blockers for the prophylaxis and therapy of coronary heart diseases. Substances such as tamoxifen are considered to be used as antiestrogen, and such as testolactone to be used as aromatase inhibitors.</p> <p>(57) Zusammenfassung</p> <p>Verwendung von Antiöstrogenen und Aromatasehemmern, gegebenenfalls in Kombination mit <math>\beta</math>-Rezeptorenblockern, zur Prophylaxe und Therapie von koronaren Herzkrankheiten. Als Antiöstrogenen kommen Substanzen wie Tamoxifen und als Aromatasehemmer solche wie Testolacton infrage.</p>		

Prophylaxe und Therapie von koronaren  
Herzkrankheiten durch Senkung des Östrogenspiegels

Die Erfindung betrifft die Prophylaxe und Therapie von koronaren Herzkrankheiten durch Senkung des Östrogenspiegels. Koronare Herzkrankheiten gehören zu den häufigsten lebensbedrohenden Gefäßerkrankungen. Zur Behandlung dieser Krankheiten verwendet man mehrere Präparate, die einmal auf das Gefäßsystem erweiternd wirken, die die gestörte Sauerstoffversorgung des Herzmuskelgewebes (Myocard) verbessern und die dazu noch die Bildung von Blutgerinnseln (Thrombozytenaggregation) verhindern sollen. Darüber hinaus wird auch der Blutdruck medikamentös gesenkt.

Obwohl seit vielen Jahren bekannt ist, daß Männer mit koronaren Herzkrankheiten wie Angina pectoris, Koronarinsuffizienz, drohendem oder eingetretenem Herzinfarkt im Serum erhöhte Östrogenspiegel aufweisen, hat man noch niemals versucht, eine Behandlung vorzunehmen, bei der der Östrogenspiegel gesenkt wird.

Eine Behandlung durch Senkung des Östrogenspiegels wurde bisher nur bei Erkrankungen endokriner Drüsen vorgeschlagen, zum Beispiel bei Mammakarzinom (US-Patent 4.235.893, Endocrinology 100 (1977) 1684 - 1695), Prostatahyperplasie (DE-OS 2 817 157 und DE-OS 3 121 153) oder Oligospermie (J. Clin. End. and Met. 52 (1981) 897 - 902).

Zur Senkung des Östrogenspiegels kommen Antiöstrogene wie Tamoxifen und insbesondere Aromatasehemmer wie Testolacton infrage.



Man hat festgestellt, daß der Serumöstradiolspiegel bei Männern mit koronaren Herzkrankheiten signifikant höher liegt als bei gesunden Männern (The American Journal of Medicine 74 (1983) 863 - 869). Ebenso sind die Serum-östrogenspiegel bei Männern mit akutem Herzinfarkt erhöht (The American Journal of Medicine 73 (1982) 872 - 881).

Ferner ist bekannt, daß Aromatasehemmer den Östrogen-gehalt im Plasma senken (J. Clin. and Met. 52 (1981) 897 - 902).

Es wurde nun gefunden, daß durch Verabreichung von Aromatasehemmern auch der Östrogengehalt im Herzvorhof (Atrium cordis) vermindert werden kann.

Behandelt man geriatrische Rattenböcke (Alter ca. 2 Jahre) über 8 Tage subkutan mit einem Aromatasehemmer, wie zum Beispiel täglich 6 mg 4-Hydroxy-4-androsten-3,17-dion, und senkt damit den Östrogengehalt im Plasma, so findet man nach Gabe von (<sup>3</sup>H)-Östradiol einen überraschenden Anstieg der Tritiumaufnahme im Atrium gegenüber einer nicht mit 4-Hydroxy-4-androsten-3,17-dion behandelten Kontrollgruppe. Hieraus läßt sich schließen, daß der Aromatasehemmer den Östrogenspiegel insgesamt im Organismus senkt und damit auch den Einbau von Östrogenen im Atrium vermindert. Mit der dann folgenden Zugabe von spezifisch hoch Tritium-markiertem Östradiol (1 µg 3,17-Dihydroxy-1,3,5(10)-/2,4,6,7,16,17-<sup>3</sup>H-estratrien) findet eine bevorzugte Aufnahme in die an Östrogen verarmten Östrogenrezeptoren im Atrium statt. Der Faktor der Anreicherung gegenüber der Kontrollgruppe beträgt 3 und bestätigt damit die hohe Bedeutung, die im Zusammenhang zwischen Östrogenspiegel im Plasma, Östrogenaufnahme im Herzmuskel und koronaren Erkrankungen gegeben ist.



Erste Ergebnisse einer Nacharbeitung einer in Science 196 (1977) 319 - 321 publizierten Arbeit von Stumpf et al. zeigen nach Applikation von (<sup>3</sup>H)-Östradiol bei nicht vorbehandelten 2 Jahre alten Rattenböcken einen etwa 3fach höheren Östrogengehalt im Atrium als in anderen Teilen des Herzens oder im Plasma.

Aus in vitro-Untersuchungen zur Aromatasehemmwirkung mit  $\beta$ -Rezeptoren-Blockern in Sertoli-Zellen (Molecular and Cellular Endocrinology, 13 (1979) 241 - 253) ist bekannt, daß eine durch Inkubation mit Testosteron und Stimulation mit Epinephrin um den Faktor 9 verstärkte Bildung von Östradiol durch Zusatz von Propranolol auf das 2fache der Östradiolbildung gegenüber der Kontrollgruppe abfällt.

In neuen von V. Hansson, Oslo, durchgeführten in vitro-Studien wurde nun gefunden, daß sowohl  $\beta$ -Rezeptoren-blocker, wie Propranolol und Mepindolol, als auch Aromatasehemmer, wie Testolacton und 4-Hydroxy-4-androsten-3,17-dion, in Sertoli-Zellkulturen eine durch Isoproterenol induzierte Aromatisierung zu hemmen vermögen. Hier bietet sich eine Parallele in der Wirkungsweise von  $\beta$ -Blockern und Aromatasehemmern an. Wenn auch der biochemische Angriffspunkt im Ablauf der Ereignisse, die zur Aromatisierung führen, ein anderer ist, so bleibt letztlich beiden Stoffklassen gemeinsam eine Minderung des endogenen Östrogengehalts.

Aus den Ergebnissen der Studien von Hansson läßt sich folgern, daß die Aromatasehemmwirkung - mit ihrer Konsequenz einer verminderten Östrogenbildung - auch das Wirkprofil der  $\beta$ -Blocker prägt. So wie Isoproterenol sollte auch Adrenalin (Epinephrin) die Aromatisierung induzieren.  $\beta$ -Blocker greifen zweimal in den Östrogenbildungsregelmechanismus ein. Einmal über eine verminderte



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Adrenalinausschüttung per se und Blockierung des Angriffspunktes von Adrenalin ( $\beta$ -Receptoren) und der damit geringeren Stimulierung einer Aromatisierung und zum anderen über die nachgewiesene sekundäre Hemmwirkung auf die als Folge der Stimulierung anlaufende Aromatisierung.

Erste klinische Versuche mit dem Aromatasehemmer Testolacton bei Patienten mit koronaren Herzkrankheiten sind vielversprechend.

In einem Fall ließen Angina-pectoris-Beschwerden schon nach 4wöchiger Einnahme von täglich je 2 mal 100 mg Testolacton nach und verschwanden schließlich völlig. Das durch Krampf- und Angstzustände gekennzeichnete Krankheitsbild wurde vom Patienten nicht mehr empfunden. Die Therapie wurde 5 Monate fortgesetzt. In dieser Zeit traten nur noch einmal kurzfristig Herzbeschwerden auf, die jedoch den früheren schmerzhaften Schweregrad nicht erreichten.

Auch nach Absetzen des Testolactons blieben die Beschwerden aus, und der Patient ist weiterhin - nach Ablauf von weiteren 8 Monaten - beschwerdefrei. Da ein lebensbedrohender Zustand nicht vorlag, kann mit der Medikation so lange ausgesetzt werden, bis erneut Beschwerden eintreten, die dann nach Einsatz einer Erhaltungsdosis wieder zum Verschwinden gebracht werden können.

Die Dosierung des Antiöstrogens bzw. des Aromatasehemmers richtet sich nach der Art und Schwere der Herzkrankheit. Im allgemeinen wird man mit einer täglichen Dosis eines Antiöstrogens, die der von 10 bis 200 mg Tamoxifen entspricht, oder eines Aromatasehemmers, die der von 50 bis 1000 mg Testolacton entspricht, auskommen.



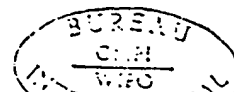
Zur Prophylaxe und Therapie von koronaren Herzkrankheiten sind erfindungsgemäß alle Stoffe geeignet, die eine Senkung des Östrogenspiegels bewirken. Zu diesen Stoffen zählen alle Antiöstrogene, die sowohl steroidal als auch nicht-steroidal sein können. Zu den am besten untersuchten nicht-steroidalen Antiöstrogenen zählen:

Tamoxifen ((Z)-2-/ $\bar{p}$ -(1,2-Diphenyl-1-butenyl)-phenoxy)-N,N-dimethylethylamin) und dessen Salze,  
Clomifen (1-/ $\bar{p}$ -( $\beta$ -diethylaminoethoxy)phenyl)-1,2-diphenylchloroethylen,  
Cyclofenil (Bis(p-acetoxyphenyl)cyclohexylidenmethan,  
Nafoxidin (1-(2-/ $\bar{4}$ -(6-Methoxy-2-phenyl-3,4-dihydro-1-naphthyl)phenoxy)-ethyl)-pyrrolidin, hydrochlorid u.a.

Als Beispiele für steroidale Antiöstrogene seien 11 $\alpha$ -Methoxy-17 $\alpha$ -ethinyl-östradiol und 16 $\beta$ -Ethylöstradiol genannt.

Ein Übersichtsreferat über die "Pharmalogie der Anti-östrogene", in dem noch weitere Antiöstrogene abgehandelt werden, ist publiziert in "Gynäkologe" 12 (1979) 199 - 211, Springer-Verlag.

Da die beim Manne vorhandenen Östrogene vorwiegend aus der peripheren Aromatisierung von androgenen Hormonen stammen (Excerpta Medica 1979, 42 - 50 und J. Clin. Endocrinol. Metab. 27 (1967) 1103 - 1111), sind Aromatasehemmer zur Senkung des Östrogenspiegels beim Manne besonders gut geeignet. Durch Verabreichung von Aromatasehemmern wird die Bildung von biologisch wirksamen Östrogenen (Östrogenbiosynthese) verhindert bzw. gehemmt. Erfindungsgemäß sind alle Aromatasehemmer geeignet, die die Östrogenbiosynthese hemmen und selbst nur geringe oder keine östrogene oder andere hormonelle Wirkung entfalten. Aromatasehemmer gemäß



vorliegender Erfindung sind zum Beispiel  
Testolacton (17a-Oxa-D-homo-androsta-1,4-dien-3,17-dion,  
Androst-4-en-4-ol-3,17-dion (Endocrinology 100 (1977)  
1634 - 1695),  
Ester des Androst-4-en-4-ol-3,17-dions (US-Patent 4 235 393).

Weitere geeignete Aromatasehemmer werden beschrieben  
beispielsweise in Endocrinology 92 (1973) 866 - 880,  
DE-OS 3 124 719 und US-Patent 4 239 762.

Die Erfindung betrifft auch Mittel zur Senkung des Östro-  
genspiegels für die Prophylaxe und Therapie von koronaren  
Herzkrankheiten bei Männern, wobei Antiöstrogene und ins-  
besondere Aromatasehemmer zur Senkung des Östrogenspiegels  
geeignet sind.

Die Wirkstoffe (Östrogenspiegelsenker) können mit den in  
der galenischen Pharmazie üblichen Zusätzen, Trägersub-  
stanzen und/oder Geschmackskorrigentien nach an sich be-  
kannten Methoden zu den üblichen Applikationsformen ver-  
arbeitet werden, beispielsweise für die orale, perkutane  
oder parenterale Applikation.

Für die bevorzugte orale Applikation kommen insbesondere  
Tabletten, Dragées, Kapseln, Pillen, Suspensionen oder  
Lösungen infrage.

Die wie oben angegeben formulierten Arzneimittel enthalten  
vorzugsweise

10 - 100 mg Tamoxifen oder biologisch äquivalente Mengen  
eines anderen Antiöstrogens oder  
50 - 200 mg Testolacton oder biologisch äquivalente Mengen  
eines anderen Aromatasehemmers.





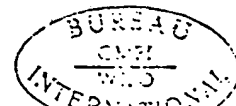
- 7 -

Darüber hinaus können zur Behandlung von Herzkrankheiten gemäß vorliegender Erfindung auch Antiöstrogene oder Aromatasehemmer mit  $\beta$ -Rezeptorenblockern gemeinsam verabreicht werden. Antiöstrogene und  $\beta$ -Rezeptorenblocker oder Aromatasehemmer und  $\beta$ -Rezeptorenblocker werden vorzugsweise gleichzeitig in getrennten oder einheitlichen Dosiseinheiten appliziert.

$\beta$ -Rezeptorenblocker werden zusammen mit Antiöstrogenen oder Aromatasehemmern in gleicher Form und gleicher oder bis auf die Hälfte herabgesetzter Menge im Vergleich zu der Behandlung mit  $\beta$ -Blockern allein appliziert.

Das Gewichtsverhältnis von Aromatasehemmer zu  $\beta$ -Blocker liegt für Testolacton als Aromatasehemmer und Propranolol als  $\beta$ -Blocker etwa bei 1 : 1 bis 15 : 1. Je nach der Wirkungsstärke der Wirkstoffe kann das Gewichtsverhältnis der Kombination entsprechend angepaßt werden.

Als  $\beta$ -Rezeptorenblocker sind außer Propranolol auch alle anderen bekannten  $\beta$ -Blocker geeignet, wie zum Beispiel Oxprenolol, Nadolol, Pindolol, Mepindolol, Sotalol usw.



## Beispiel 1

100,0 mg	17a-Oxa-D-homoandrosta-1,4-dien-3,17-dion (Testolacton)
80,5 mg	Lactose
39,5 mg	Maisstärke
2,5 mg	Poly-N-Vinylpyrrolidon 25
2,0 mg	Aerosil
<u>0,5 mg</u>	Magnesiumstearat
225,0 mg	Gesamtgewicht der Tablette, die in üblicher Weise auf einer Tablettenpresse hergestellt wird.

## Beispiel 2

50,0 mg	17a-Oxa-D-homoandrosta-1,4-dien-3,17-dion (Testolacton)
115,5 mg	Lactose
54,5 mg	Maisstärke
2,5 mg	Poly-N-Vinylpyrrolidon 25
2,0 mg	Aerosil
<u>0,5 mg</u>	Magnesiumstearat
225,0 mg	Gesamtgewicht der Tablette, die in üblicher Weise auf einer Tablettenpresse hergestellt wird.



## Beispiel 3

Zusammensetzung einer öligen Lösung:

50,0 mg 17a-Oxa-D-homoandrosta-1,4-dien-3,17-dion  
(Testolacton)  
378,4 mg Rizinusöl  
643,6 mg Benzylbenzoat  
1072,0 mg  $\hat{=}$  1 ml Lösung

Die Lösung wird in eine Ampulle gefüllt und sterilisiert.

## Beispiel 4

Zusammensetzung einer Tablette:

20,0 mg (Z)-2-/ $\bar{p}$ -(1,2-Diphenyl-1-butenyl)-phenoxy7-  
N,N-dimethyläthylamin (Tamoxifen)  
120,5 mg Lactose  
59,5 mg Maisstärke  
2,5 mg Poly-N-Vinylpyrrolidon 25  
2,0 mg Aerosil  
0,5 mg Magnesiumstearat  
205,0 mg Gesamtgewicht der Tablette, die in üblicher Weise  
auf einer Tablettenpresse hergestellt wird.



Patentansprüche

- 1.) Mittel zur Senkung des Östrogenspiegels für die Prophylaxe und Therapie von koronaren Herzkrankheiten bei Männern.
- 2.) Mittel nach Anspruch 1 auf Basis eines Antiöstrogens, gegebenenfalls in Kombination mit einem  $\beta$ -Rezeptorenblocker.
- 3.) Mittel nach Anspruch 1 auf Basis eines Aromatasehemmers, gegebenenfalls in Kombination mit einem  $\beta$ -Rezeptorenblocker.
- 4.) Mittel nach Anspruch 1 in einer oralen Applikationsform.
- 5.) Mittel nach Anspruch 1 für die perkutane oder parenterale Applikation.
- 6.) Mittel nach Anspruch 1, enthaltend 10 - 100 mg Tamoxifen oder biologisch äquivalente Mengen eines anderen Antiöstrogens.
- 7.) Mittel nach Anspruch 1, enthaltend 50 - 200 mg Testolacton oder biologisch äquivalente Mengen eines anderen Aromatasehemmers.
- 8.) Prophylaxe und Therapie von koronaren Herzkrankheiten bei Männern durch Senkung des Östrogenspiegels.
- 9.) Verwendung von Antiöstrogenen, gegebenenfalls in Kombination mit  $\beta$ -Blockern zur Prophylaxe und Therapie von koronaren Herzkrankheiten nach Anspruch 8.



- 10.) Verwendung von Tamoxifen gemäß Anspruch 9.
- 11.) Verwendung von täglich 10 - 200 mg Tamoxifen bzw. biologisch äquivalente Mengen eines anderen Anti-östrogens nach Anspruch 9.
- 12.) Verwendung von Aromatasehemmern, gegebenenfalls in Kombination mit  $\beta$ -Blockern, zur Prophylaxe und Therapie von koronaren Herzkrankheiten nach Anspruch 8.
- 13.) Verwendung von Testolacton gemäß Anspruch 12.
- 14.) Verwendung von täglich 50 - 1000 mg Testolacton bzw. biologisch äquivalente Mengen eines anderen Aromatasehemmers nach Anspruch 12.



# INTERNATIONAL SEARCH REPORT

International Application No PCT/DE 84/00137

## I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) \*

According to International Patent Classification (IPC) or to both National Classification and IPC

Int. Cl.<sup>3</sup> : A 61 K 31/13; A 61 K 31/365

## II. FIELDS SEARCHED

Minimum Documentation Searched \*

Classification System

Classification Symbols

Int. Cl.<sup>3</sup>

A 61 K 31/00

Documentation Searched other than Minimum Documentation  
to the extent that such Documents are included in the Fields Searched \*

## III. DOCUMENTS CONSIDERED TO BE RELEVANT <sup>14</sup>

Category *	Citation of Document, <sup>15</sup> with indication, where appropriate, of the relevant passages <sup>17</sup>	Relevant to Claim No. <sup>18</sup>
X	GB. A. 2078749 (MERRELL DOW) 13 January 1982, see page 1, in particular lines 22,23	1-4.8.9.12.14
X	US. A. 4289762 (B.W.METCALF) 15 September 1981, see column 2, lines 65-68; column 3, lines 1,2	1-4.8.9.12.14
X	LU. A. 83544 (SCHERING AG) 01 December 1981, see claims	3.7.12-14
X	The Merck Index, tenth edition, published in 1983, see page 1300, compound 8923; page 1312, compound 8999	6.7.10.12-14

\* Special categories of cited documents: <sup>16</sup>

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

## IV. CERTIFICATION

Date of the Actual Completion of the International Search \*

13 September 1984 (13.09.84)

Date of Mailing of this International Search Report \*

01 October 1984 (01.10.84)

International Searching Authority \*

European Patent Office

Signature of Authorized Officer <sup>19</sup>

# ANNEX TO THE INTERNATIONAL SEARCH REPORT ON

INTERNATIONAL APPLICATION NO. PCT/DE 84/00137 (SA 7403)

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 25/09/84

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB-A- 2078749	13/01/82	BE-A- 889401	23/12/81
		FR-A, B 2485543	31/12/81
		NL-A- 8103101	18/01/82
		JP-A- 57038797	03/03/82
		US-A- 4322416	30/03/82
		SE-A- 8103963	23/12/81
		AU-A- 7237081	07/01/82
		DE-A- 3124780	03/06/82
		CA-A- 1173431	23/08/84
		GB-A- 2135314	30/08/84
US-A- 4289762	15/09/81	BE-A- 889404	23/12/81
		GB-A- 2078750	13/01/82
		FR-A, B 2485544	31/12/81
		NL-A- 8103098	13/01/82
		JP-A- 57038798	03/03/82
		DE-A- 3124719	13/03/82
		SE-A- 8103988	23/12/81
		AU-A- 7236981	07/01/82
		CA-A- 1173432	23/08/84
LU-A- 83544	01/12/81	BE-A- 890521	23/03/82
		DE-A- 3121153	09/12/82
		JP-A- 57193411	27/11/82
		GB-A- 2100601	06/01/83
		NL-A- 8103874	15/12/82
		AU-A- 8407482	25/11/82

For more details about this annex :  
see Official Journal of the European Patent Office, No. 12/82

# INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen

PCT/DE 84/00137

<b>I. KLASSEFIZIKATION DES ANMELDUNGS-GEGENSTANDS</b> (bei mehreren Klassifikationssymbolen sind alle anzugeben) Nach der internationalen Patentklassifikation (IPC) oder nach der nationalen Klassifikation und der IPC		
Int.Kl. <sup>3</sup> : A 61 K 31/13; A 61 K 31/365		
<b>II. RECHERCHIERTE SACHGEBIETE</b>		
Recherchierter Mindestprüfstoff <sup>4</sup>		
Klassifikationssystem	Klassifikationssymbole	
Int.Kl. <sup>3</sup>	A 61 K 31/00	
Recherchierte nicht zum Mindestprüfstoff gehörende Veröffentlichungen, soweit diese unter die recherchierten Sachgebiete fallen <sup>5</sup>		
<b>III. EINSCHLAGIGE VERÖFFENTLICHUNGEN<sup>6</sup></b>		
Art <sup>7</sup>	Kennzeichnung der Veröffentlichung, soweit erforderlich unter Angabe der Maßgeblichen Teile <sup>8</sup>	Betr. Anspruch Nr. <sup>9</sup>
X	GB, A, 2078749 (MERRELL DOW) 13. Januar 1982, siehe Seite 1, insbesondere Zeilen 22,23	1-4,8,9,12,14
X	US, A, 4289762 (B.W. METCALF) 15. September 1981, siehe Spalte 2, Zeilen 65-68; Spalte 3, Zeilen 1,2	1-4,8,9,12,14
X	LU, A, 83544 (SCHERING AG) 1. Dezember 1981, siehe Ansprüche	3,7,12-14
X	The Merck Index, tenth edition, veröffentlicht in 1983, siehe Seite 1300, compound 8923; Seite 1312, compound 8999	6,7,10,12-14
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<p><sup>1</sup> Besondere Kategorien von angegebenen Veröffentlichungen<sup>10</sup>:</p> <p>"A" Veröffentlichung, die den allgemeinen Stand der Technik definiert, aber nicht als besonders bedeutsam anzusehen ist</p> <p>"E" älteres Dokument, das jedoch erst am oder nach dem internationalen Anmeldedatum veröffentlicht worden ist</p> <p>"L" Veröffentlichung, die geeignet ist, einen Prioritätsanspruch zweifelhaft erscheinen zu lassen, oder durch die das Veröffentlichungsdatum einer anderen im Recherchenbericht genannten Veröffentlichung belegt werden soll oder die aus einem anderen besonderen Grund angegeben ist (wie aus- geführt)</p> <p>"O" Veröffentlichung, die sich auf eine mündliche Offenbarung, eine Ausstellung, eine Ausstellung oder andere Maßnahmen bezieht</p> <p>"P" Veröffentlichung, die vor dem internationalen Anmeldedatum, aber nach dem beanspruchten Prioritätsdatum veröffentlicht worden ist</p> <p>"S" Spätere Veröffentlichung, die nach dem internationalen Anmeldedatum oder dem Prioritätsdatum veröffentlicht worden ist, aber mit der Anmeldung nicht kollidiert, sondern nur zum Verständnis des der Erfindung zugrundeliegenden Prinzips oder der ihr zugrundeliegenden Theorie angegeben ist</p> <p>"X" Veröffentlichung von besonderer Bedeutung: die beanspruchte Erfindung kann nicht als neu oder auf erfindungs- föhrer Tätigkeit beruhend betrachtet werden</p> <p>"Y" Veröffentlichung von besonderer Bedeutung: die beanspruchte Erfindung kann nicht als auf erfindungs- föhrer Tätigkeit beruhend betrachtet werden, wenn die Veröffentlichung mit einer oder mehreren anderen Veröffentlichungen dieser Kategorie in Verbindung gebracht wird und diese Verbindung für einen Fachmann naheliegend ist</p> <p>"Z" Veröffentlichung, die Mitglied derselben Patentfamilie ist</p>		
<b>IV. BESCHEINIGUNG</b>		
Datum des Abschlusses der internationalen Recherche <sup>11</sup>		Veröffentlichungsdatum des internationalen Recherchenberichts <sup>12</sup>
13. September 1984		01 OCT. 1984
Internationale Recherchenanträge <sup>13</sup>		Unterschrift des bevollmächtigten Recherchenberichts <sup>14</sup>
Europäisches Patentamt		G.L.M. KRUYDENBERG



# ANHANG ZUM INTERNATIONALEN RECHERCHENBERICHT UBER DIE

INTERNATIONALE PATENTANMELDUNG NR. PCT/DE 84/00137 (SA 7403)

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentedokumente angegeben. Die Angaben über die Familienmitglieder entsprechen dem Stand der Datei des Europäischen Patentamts am 25/09/84

Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

Im Recherchenbericht angeführtes Patentedokument	Datum der Veröffentlichung	Mitglied(er) der Patentfamilie	Datum der Veröffentlichung
GB-A- 2078749	13/01/82	BE-A- 889401	29/12/81
		FR-A,B 2485543	31/12/81
		NL-A- 8103101	18/01/82
		JP-A- 57038797	03/03/82
		US-A- 4322416	30/03/82
		SE-A- 8103963	28/12/81
		AU-A- 7237081	07/01/82
		DE-A- 3124780	03/06/82
		CA-A- 1173431	28/08/84
		GB-A- 2135314	30/08/84
US-A- 4289762	15/09/81	BE-A- 889404	29/12/81
		GB-A- 2078750	13/01/82
		FR-A,B 2485544	31/12/81
		NL-A- 8103098	18/01/82
		JP-A- 57038798	03/03/82
		DE-A- 3124719	18/03/82
		SE-A- 8103988	28/12/81
		AU-A- 7236981	07/01/82
		CA-A- 1173432	28/08/84
LU-A- 83544	01/12/81	BE-A- 890521	29/03/82
		DE-A- 3121153	09/12/82
		JP-A- 57193411	27/11/82
		GB-A- 2100601	06/01/83
		NL-A- 9103874	15/12/82
		AU-A- 8407482	25/11/82

Für nähere Einzelheiten zu diesem Anhang :  
siehe Amtsblatt des Europäischen Patentamts, Nr. 12/82

Code: 1147-20532

WORLD PATENT  
WORLD INTELLECTUAL PROPERTY ORGANIZATION  
INTERNATIONAL OFFICE

INTERNATIONAL APPLICATION PUBLISHED ON THE BASIS OF THE PATENT  
COOPERATION TREATY (PCT)

International Publication No. WO 85/00107  
International Cl.<sup>3</sup>: A61K 31/13, 31/365  
International Application No.: PCT/DE84/00137  
International Filing Date: June 19, 1984 (6-19-84)  
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Priority:  
    Priority No.: P 3,323,321.7  
    Priority Date: June 24, 1983 (6-24-83)  
    Priority Country: Federal Republic of Germany  
Treaty Nations Cited: Federal Republic of Germany  
    (European Patent),  
    France (European Patent),  
    Great Britain (European Patent),  
    Japan,  
    Netherlands (European Patent),  
    United States of America

PROPHYLAXIS AND TREATMENT OF CORONARY HEART DISEASE BY  
LOWERING THE ESTROGEN LEVEL

Applicant (applicable to all  
treaty nations cited except  
for the United States of

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Published with the International Search Report

Utilisation of antiestrogen and aromatase inhibitors, optionally in combination with  $\beta$ -receptor blockers for the prophylaxis and therapy of coronary heart diseases. Substances such as tamoxifen are considered to be used as antiestrogen, and such as testolactone to be used as aromatase inhibitors.

The subject matter of this invention concerns the prophylaxis and treatment of coronary heart disease by lowering the estrogen level. Coronary heart disease is among the most frequently encountered life-threatening vascular diseases. In the treatment of these diseases, several drugs are used, which, first of all, have a dilatory effect on the vascular system, which improve the impaired oxygen supply to the tissue of the cardiac muscle (myocardium), and which are also supposed to prevent the formation of blood clots (platelet aggregation). In addition, the blood pressure is lowered by administering appropriate drugs.

In spite of the fact that it has been known for many years that men who suffer from coronary heart disease, such as angina pectoris, coronary insufficiency, cardiac infarction either impending or already occurred, have increased estrogen levels in the serum, it has never been attempted to treat them by lowering the estrogen level.

So far, a treatment by lowering the estrogen level has been proposed only for diseases of the endocrine glands, for example, for breast cancer (U.S. Patent No. 4,235,893, Endocrinology 100 (1977), 1684-1695), for prostatic hypertrophy ([West] German Patent Applications [Offenlegungsschrift] No. 2,817,157 and No. 3,121,153), or for oligospermia (J. Clin. End. and Met. 52 (1981), 897-902).

To lower the estrogen level, antiestrogens, such as tamoxifen, and especially aromatase inhibitors, such as testolactone, can be used.

It has been discovered that in men with coronary heart disease, the serum estradiol level is significantly higher than in healthy men (The American Journal of Medicine 74 (1983), 863-869). Similarly, the serum estradiol levels of men with acute cardiac infarction are increased (The American Journal of Medicine 73 (1982), 872-881).

It is also well-known that aromatase inhibitors reduce the estrogen concentration in the plasma (J. Clin. End. and Met. 52 (1981), 897-902).

It was discovered that the estrogen concentration in the atrium of the heart (atrium cordis) can also be lowered by administering aromatase inhibitors.

When male geriatric rats (approximately 2 years old) are subcutaneously treated for 8 days with an aromatase inhibitor, for example, with 6 mg of 4-hydroxy-4-androstene-3,17-dione per day, thus lowering the estrogen concentration in the plasma, a surprising increase of the tritium absorption in the atrium is found after administration of (<sup>3</sup>H)-estradiol when this group of rats is compared to a control group that had not been treated with 4-hydroxy-4-androstene-3,17-dione. This indicates that the aromatase inhibitor lowers the estrogen level in the entire organism and thus reduces the incorporation of estrogens in the atrium. When estradiol, which is labeled with specifically high tritium (1 µg of 3,17-dihydroxy-1,3,5(10)-[2,4,6,7,16,17-<sup>3</sup>H]-estratriene, is subsequently administered, a preferred absorption by the estrogen-depleted estrogen receptors in the atrium occurs. Compared to the control group, the factor of accumulation is 3, which confirms the high significance of the correlation between

estrogen level in the plasma, the estrogen found in the cardiac muscle, and coronary heart disease.

Preliminary results of a test which duplicated the work published by Stumpf et al. in Science 196 (1977), 319-321, show that after administering (<sup>3</sup>H)-estradiol to 2-year-old male rats which had not been pretreated, the estrogen concentration in the atrium is approximately 3 times higher than in other parts of the heart or in the plasma.

It is known from in-vitro studies of the effect of aromatase inhibition with  $\beta$ -receptor blockers in Sertoli cells (Molecular and Cellular Endocrinology 13 (1979, 241-253) that the formation of estradiol, which has been increased by a factor of 9 by incubation with testosterone and stimulation with epinephrine, decreases by the addition of propranolol to twice the estradiol formation when compared to the control group.

In new in-vitro studies which were carried out by V. Hansson in Oslo, it was found that  $\beta$ -receptor blockers, such as propranolol and mepindolol, as well as aromatase inhibitors, such as testolactone and 4-hydroxy-4-androstene-3,17-dione, are able to inhibit an aromatization induced by isoproterenol in Sertoli cell cultures. This points to a parallel mechanism of action of the  $\beta$ -blockers and the aromatase inhibitors. Although the biochemical points of attack in the course of the events which lead to the aromatization differ, in the final analyses, the two substances have a common effect, namely that of lowering the endogenous estrogen level.

The results of the studies by Hansson indicate that the effect of aromatase inhibition -- which entails a reduced

estrogen formation -- also characterizes the profile of the mechanism of action of the  $\beta$ -blockers. Adrenaline (epinephrine), like isoproterenol, should also induce aromatization.  $\beta$ -Blockers interfere at two different points with the mechanism that controls the estrogen formation: first, through the reduction of the adrenaline production as such and the blockage of the point of attack of adrenaline ( $\beta$ -receptors) and the thus reduced stimulation of an aromatization, and secondly, through the proven secondary inhibitory effect on the aromatization which begins as a result of the stimulation.

Preliminary clinical tests with the aromatase inhibitor testolactone in patients with coronary heart disease look very promising.

In one case, angina pectoris symptoms decreased as early as after 4 weeks of 100 mg of testolactone twice a day and finally disappeared completely. The patient whose clinical picture had been characterized by spasmodic and anxiety fits no longer suffered these symptoms. The therapy was continued for 5 months. During this time, heart problems occurred only once and for a short time only but never reached the degree of severe pain the patient had felt previously.

Even after discontinuing the treatment with testolactone, the symptoms were absent, and -- after 8 more months -- the patient continues to be symptom-free. When the condition of the patient is not life-threatening, it is possible to stop the medication until the symptoms appear again. Subsequently, a maintenance dose can be used to cause the symptoms to disappear once again.

The antiestrogen or aromatase inhibitor dose depends on the type and severity of the coronary heart disease. Generally, a daily dose of an antiestrogen, which corresponds to 10 to 200 mg of tamoxifen, or an aromatase inhibitor, which corresponds to 50 to 1000 mg of testolactone, suffices.

To prevent and treat coronary heart disease, all substances which cause a lowering of the estrogen level can be used according to this invention. These substances include all antiestrogens which may be either steroidal or nonsteroidal. The most thoroughly studied nonsteroidal antiestrogens include:

tamoxifen ((Z)-2-[p-(1,2-diphenyl-1-butenyl)phenoxy]-N,N-dimethylethanamine) and its salts,  
 clomiphene (1-[p-( $\beta$ -dimethylaminoethoxy)phenyl]-1,2-diphenylchloroethylene,  
 cyclofenil (Bis(p-acetoxyphenyl)cyclohexylidenemethane,  
 nafoxidine (1-(2-[4-(6-methoxy-2-phenyl-3,4-dihydro-1-naphthyl)-phenoxy]ethyl)pyrrolidine hydrochloride, etc.

Examples of steroidal antiestrogens include 11 $\alpha$ -methoxy-17 $\alpha$ -ethinyl estradiol and 16 $\beta$ -ethyl estradiol.

A survey with the title "Pharmacology of antiestrogens," in which other antiestrogens are described, has been published in Gynäkologe 12 (1979), 199-211, Springer Verlag.

Since the estrogens present in men are derived mainly from the peripheral aromatization of androgenous hormones (Excerpta Medica 1979, 42-50, and J. Clin. Endocrinol. Metab. 27 (1967), 1103-1111), aromatase inhibitors are especially well suited to lower the estrogen level in men. By administering aromatase



inhibitors, the formation of biologically effective estrogens (estrogen biosynthesis) is prevented or inhibited. According to this invention, all aromatase inhibitors, which inhibit the estrogen biosynthesis and which have only an insignificant or no estrogenic or other hormonal effect, can be used. Aromatase inhibitors according to this invention include, for example, testolactone (D-homo-17 $\alpha$ -oxaandrosta-1,4-diene-3,17-dione), androst-4-en-4-ol-3,17-dione (Endocrinology 100 (1977), 1684-1695), and esters of androst-4-en-4-ol-3,17-dione (U.S. Patent No. 4,235,893).

Other suitable aromatase inhibitors are described, for example, in Endocrinology 92 (1973), 866-880, in the [West] German Patent Application [Offenlegungsschrift] No. 3,124,719, and in the U.S. Patent No. 3,239,762.

The subject matter of this invention also concerns substances for lowering the estrogen level to prevent and to treat coronary heart disease in men; particularly suitable for lowering the estrogen level are antiestrogens and especially aromatase inhibitors.

The active substances (estrogen level lowering drugs) may be processed according to well-known methods in combination with the additives, vehicles and/or flavor enhancers normally used in galenic pharmacy to produce drugs for the conventional types of administration, such as oral, percutaneous, or parenteral administration.

For oral administration which is preferred, especially tablets, dragées, capsules, pills, suspensions, or solutions can be used.

The drugs formulated as described above preferably contain 10-100 mg of tamoxifen or biologically equivalent quantities of another type of antiestrogen or 50-200 mg of testolactone or biologically equivalent quantities of another type of aromatase inhibitor.

In addition, according to this invention, antiestrogens or aromatase inhibitors may also be used in combination with  $\beta$ -receptor blockers to treat coronary heart disease. Antiestrogens and  $\beta$ -receptor blockers or aromatase inhibitors and  $\beta$ -receptor blockers are preferably administered at the same time in separate dose units or in the same dose unit.

$\beta$ -Receptor blockers in combination with antiestrogens or aromatase inhibitors are administered in a form and in a quantity identical to or reduced by up to one half of the quantity used in the treatment with  $\beta$ -blockers alone.

The weight ratio between aromatase inhibitor and  $\beta$ -blocker is approximately 1:1 to 15:1 for testolactone as the aromatase inhibitor and for propranolol as the  $\beta$ -blocker. Depending on the efficacy of the active substances, the weight ratio of the combination can be appropriately adjusted.

In addition to propranolol as the  $\beta$ -receptor blocker, it is possible to also use other well-known  $\beta$ -blockers, such as oxprenolol, nadolol, pindolol, mepindolol, sotalol, etc.

**Example 1**

100.0 mg of D-homo-17 $\alpha$ -oxaandrosta-1,4-diene-3,17-dione  
(testolactone)

80.5 mg of lactose

39.5 mg of cornstarch

2.5 mg of poly-N-vinylpyrrolidone 25

2.0 mg of aerosil

0.5 mg of magnesium stearate

225.0 mg      Total weight of the tablet which is produced  
according to conventional methods on a tablet press.

**Example 2**

50.0 mg of D-homo-17 $\alpha$ -oxaandrosta-1,4-diene-3,17-dione  
(testolactone)

115.5 mg of lactose

54.5 mg of cornstarch

2.5 mg of poly-N-vinylpyrrolidone 25

2.0 mg of aerosil

0.5 mg of magnesium stearate

225.0 mg      Total weight of the tablet which is produced  
according to conventional methods on a tablet press.

**Example 3**Composition of an oily solution

50.0 mg of D-homo-17 $\alpha$ -oxaandrosta-1,4-diene-3,17-dione  
(testolactone)

378.4 mg of castor oil

643.6 mg of benzyl benzoate

1072.0 mg = 1 mL of solution

The solution is poured into a vial and sterilized.

**Example 4**Composition of a tablet

20.0 mg of (Z)-2-[p-(1,2-diphenyl-1-butenyl)phenoxy]-  
N,N-dimethylethanamine) (tamoxifen)

120.5 mg of lactose

59.5 mg of cornstarch

2.5 mg of poly-N-vinylpyrrolidone 25

2.0 mg of aerosil

0.5 mg of magnesium stearate

205.0 mg      Total weight of the tablet which is produced  
according to conventional methods on a tablet press.

### Patent claims

1. Medication for lowering the estrogen level in the prophylaxis and treatment of coronary heart disease in men.
2. Medication as claimed in Claim 1 on the basis of an antiestrogen, optionally in combination with a  $\beta$ -receptor blocker.
3. Medication as claimed in Claim 1 on the basis of an aromatase inhibitor, optionally in combination with a  $\beta$ -receptor blocker.
4. Medication as claimed in Claim 1 in a form suitable for oral administration.
5. Medication as claimed in Claim 1 for percutaneous or parenteral administration.
6. Medication as claimed in Claim 1, containing 10-100 mg of tamoxifen or biologically equivalent quantities of another type of antiestrogen.
7. Medication as claimed in Claim 1, containing 50-200 mg of testolactone or biologically equivalent quantities of another type of antiestrogen.
8. Prophylaxis and treatment of coronary heart disease in men by lowering the estrogen level.

9. Use of antiestrogens, optionally in combination with  $\beta$ -receptor blockers, to prevent and to treat coronary heart disease as claimed in Claim 8.

10. Use of tamoxifen as claimed in Claim 9.

11. Use of 10-200 mg of tamoxifen or biologically equivalent quantities of another type of antiestrogen as claimed in Claim 9.

12. Use of aromatase inhibitors, optionally in combination with  $\beta$ -receptor blockers, to prevent and to treat coronary heart disease as claimed in Claim 8.

13. Use of testolactone as claimed in Claim 12.

14. Use of 50-1000 mg of testolactone or biologically equivalent quantities of another type of aromatase inhibitor as claimed in Claim 12.

# INTERNATIONAL SEARCH REPORT

International Application No. PCT/DE 84/00137

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (If several classification symbols apply, indicate all) * According to International Patent Classification (IPC) or to both National Classification and IPC Int. Cl. <sup>3</sup> : A 61 K 31/13; A 61 K 31/365		
<b>II. FIELDS SEARCHED</b> <div style="text-align: center;">Minimum Documentation Searched *</div>		
Classification System	Classification Symbols	
Int. Cl. <sup>3</sup>	A 61 K 31/00	
Documentation Searched other than Minimum Documentation to the extent that such Documents are included in the Fields Searched *		
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT</b> 14		
Category *	Citation of Document, 15 with indication, where appropriate, of the relevant passages 17	Relevant to Claim No. 18
X	GB. A. 2078749 (MERRELL DOW) 13 January 1982, see page 1, in particular lines 22-23	1-4.8.9.12.14
X	US. A. 4289762 (B.W. METCALF); 15 September 1981, see column 2, lines 65-68; column 3, lines 1-2	1-4.8.9.12.14
X	LU. A. 83544 (SCHERING AG) 01 December 1981, see claims	3.7.12-14
X	The Merck Index, tenth edition, published in 1983, see page 1300, compound 8923; page 1312, compound 8999	6.7.10.12-14
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>* Special categories of cited documents; 15</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"A" document member of the same patent family</p> </div> </div>		
<b>IV. CERTIFICATION</b>		
Date of the Actual Completion of the International Search *	Date of Mailing of this International Search Report *	
13 September 1984 (13.09.84)	01 October 1984 (01.10.84)	
International Searching Authority *	Signature of Authorized Officer 19	
European Patent Office		

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 25/09/84

The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB-A- 2078749	13/01/82	BE-A- 889401	23/12/81
		FR-A, B 2485543	31/12/81
		NL-A- 8103101	18/01/82
		JP-A- 57038797	03/03/82
		US-A- 4322416	30/03/82
		SE-A- 8103963	23/12/81
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		CA-A- 1173431	23/08/84
		GB-A- 2135314	30/08/84
US-A- 4289762	15/09/81	BE-A- 889404	23/12/81
		GB-A- 2078750	13/01/82
		FR-A, B 2485544	31/12/81
		NL-A- 8103098	13/01/82
		JP-A- 57038798	03/03/82
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		DE-A- 3121153	09/12/82
		JP-A- 57193411	27/11/82
		GB-A- 2100601	06/01/83
		NL-A- 8103874	15/12/82
		AU-A- 8407482	25/11/82

For more details about this annex :  
see Official Journal of the European Patent Office, No. 12/82



PTO 96-0759

WORLD PATENT OFFICE  
Publication No. WO 85/00107

PROPHYLAXIS AND THERAPY OF CORONARY HEART DISEASES  
BY LOWERING THE ESTROGEN CONCENTRATION  
[Prophylaxe und Therapie von koronären Herzkrankheiten  
durch Senkung des Östrogenspiegels]

Paul Eberhard Schulze, et al.

UNITED STATES PATENT AND TRADEMARK OFFICE  
Washington, D. C. December 1995

Translated by: FLS, Inc.

- (19) WORLD PATENT OFFICE
  - (11) Publication No.: WO 85/00107
  - (12) International Patent Application
  - (21) Application No.: PCT/DE84/00137
  - (22) Application date: June 19, 1984
  - (51) IPC: A61K 31/13, 31/365
- 

Patent claims for the following countries:

- (30) Priority: June 24, 1983, DE, 3,323,321
  - (43) Publication date of application: January 17, 1985
  - (84) Designated member countries: DE FR GB JP NL US
  - (71) Applicant: SCHERING AKTIENGESELLSCHAFT (DE)
  - (72) inventors: Paul Eberhard Schulze (DE), Ulrich Kerb (DE)
- 

- (54) PROPHYLAXIS AND THERAPY OF CORONARY HEART DISEASES BY  
LOWERING THE ESTROGEN CONCENTRATION

Prophylaxis and Therapy of Coronary Heart Diseases  
by Lowering the Estrogen Concentration

/1\*

The invention concerns the prophylaxis and therapy of coronary heart diseases by lowering the estrogen concentration. Coronary heart diseases are included among the most frequently occurring life-threatening diseases of the circulatory system. Used to treat these diseases are several preparations which first have an expansive effect upon the circulatory system, improve the disturbed oxygen supply to the heart-muscle tissue (myocardium) and are in addition supposed to prevent the formation of blood clots (thrombocyte aggregations). In addition to that, the blood pressure is lowered with medication.

Although it has been known for many years that men with coronary heart diseases, such as angina pectoris, coronary insufficiency, a threatening or incipient coronary infarction exhibit an elevated estrogen level in the serum, no attempt has yet been made to undertake a treatment in which the estrogen concentration is lowered.

A treatment by lowering the estrogen concentration was thus far proposed only in the case of diseases of the endocrine glands, for example, in breast cancer (US patent 4,235,893, *Endocrinology* 100 (1977), 1684-1695, prostatic hyperplasia (DE-OS 2,817,157 and DE-OS 3,121,153) or oligospermia (*J. Clin. End. and Met.* 52 (1981), 897 - 902).

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\*Numbers in the margin indicate pagination in the foreign text.

Candidates for lowering the estrogen concentration include antiestrogens such as tamoxifen and, in particular, aromatase inhibitors such as testolactone.

It has been determined that the serum-estrogen level in men with coronary heart diseases lies significantly higher than that in healthy men (*The American Journal of Medicine* 74 (1983), 863 - 869). The serum-estrogen level is likewise elevated in the case of men with acute heart infarction (*The American Journal of Medicine* 73 (1982), 872 - 881).

It is known, moreover, that aromatase inhibitors reduce the estrogen content in the plasma (*J. Clin. and Met.* 52 (1981), 897 - 902).

It was then discovered that the estrogen content in the atrium cordis can also be reduced by administering aromatase inhibitors.

If geriatric male rats (age approximately 2 years) are treated subcutaneously for 8 days with an aromatase inhibitor, for example, with 6 mg daily of 4-hydroxy-4-androstene-3,17-dione, and the estrogen content in the plasma thus reduced, a surprising rise in the tritium uptake in the atrium takes place after administration of (<sup>3</sup>H)-estradiol, in comparison with a control group not treated with 4-hydroxy-4-androstene-3,17-dione. From that it is possible to conclude that the aromatase inhibitor reduces the overall estrogen concentration in the organism and thus also the uptake of estrogens in the atrium. A preferred uptake of estrogen in the estrogen-deprived receptors of the

atrium then takes place with the subsequent administration of specifically high tritium-marked estradiol (1  $\mu$ g of 3,17-dihydroxy-1,3,5(10)-[2,4,6,7,16,17- $^3$ H]-estratriene. The enrichment factor relative to the control group is 3 and thus confirms the great importance, in conjunction with the estrogen concentration in the plasma, of the detection of estrogen in the heart muscle and coronary diseases.

The first results of a revision of a study by Stumpf, et al., published in *Science* 196 (1977), 319 - 321, show, following application of ( $^3$ H)-estradiol, an estrogen content in the atrium of 2-year old, not previously treated, male rats approximately 3 times higher than that in other parts of the heart or in the plasma. /3

From in-vitro studies of aromatase-inhibition with  $\beta$ -receptor blockers in Sertoli cells (*Molecular and Cellular Endocrinology* 13 (1979), 241 - 253), it is known that a formation of estradiol, increased by a factor of 9 via incubation with testosterone and stimulation with epinephrine, is reduced by the addition of propranolol to 2 times the estradiol formation in comparison with the control group.

In recent in-vitro studies conducted by V. Hansson, Oslo, it was then found that both  $\beta$ -receptor blockers, such as propranolol and mepindolol, as well as aromatase inhibitors, such as testolactone and 4-hydroxy-4-androstene-3,17-dione, are able to inhibit an aromatization induced by isoproterenol in Sertoli-cell cultures. There is here a parallel in the operation of  $\beta$ -

blockers and aromatase inhibitors. Even if the biochemical point of attack in the sequence of events leading to the aromatization is a different one, both substance classes lead finally to a reduction of the endogenic estrogen content.

From the results of the studies by Hansson, it can be concluded that the aromatase inhibition - with the consequence of a reduced estrogen formation - also characterizes the activity of the  $\beta$ -blockers. Thus, like isoproterenol, adrenaline (epinephrine) should also induce aromatization.  $\beta$ -blockers intervene twice in the mechanism regulating estrogen formation. On the one hand via a reduced adrenaline release per se and blocking of the points of attack of adrenaline ( $\beta$ -receptors) and the resulting reduced stimulation of an aromatization and, on the other, by means of the demonstrated secondary inhibitive effect upon the aromatization taking place as a result of the stimulation. /4

Initial clinical tests with the aromatase inhibitor testolactone in patients with coronary heart diseases are highly promising.

In one case, complaints relating to angina pectoris decreased already after 4 weeks of taking 100 mg of testolactone twice daily and finally disappeared entirely. The disease picture, characterized by cramps and anxiety, was no longer experienced by the patient. The therapy was continued for 5 months. During this period, heart complaints occurred briefly only once, but did not reach the painful severity formerly

experienced.

The complaints failed to reappear even after discontinuation of the testolactone, and the patient remains free of pain - after an additional 8 months. Because a life-threatening condition was not present, the medication can be stopped until the reappearance of the complaints which can again be put to rest with the administration of a maintenance dose.

The dosage of the antiestrogen or aromatase inhibitor is determined by the severity of the heart disease. Generally sufficient is a daily dose of an antiestrogen corresponding to from 10 to 200 mg of tamoxifen, or of an aromatase inhibitor corresponding to from 50 to 1,000 mg of testolactone.

Suitable for the prophylaxis and therapy of coronary diseases per the invention are all substances which induce a lowering of the estrogen level. These substances include all antiestrogens, which can be both steroidal as well as nonsteroidal. The most thoroughly studied nonsteroidal antiestrogens include:

Tamoxifen ((Z)-2-[p-1,2-diphenyl-1-butenyl)-phenoxy]-N,N-dimethylamine) and its salts, clomifene (1-[p-[ $\beta$ -diethylaminoethoxy)phenyl]-1,2-diphenylchloroethylene, cyclofenil (bis-(p-acetoxyphenyl)cyclohexylidenemethane, nafoxidine (1-(2-[4-6-methoxy-2-phenyl-3,4-dihydro-1-naphthyl)phenoxy]-ethyl)-pyrrolidine, hydrochloride, etc.

Examples of steroidal antiestrogens include 11 $\alpha$ -methoxy-17 $\alpha$ -ethinylestradiol and 16 $\alpha$ -ethylestradiol.

A summary lecture on the "Pharmacology of the Antiestrogens", in which still further antiestrogens are discussed, was published in *Gynäkologe* 12 (1979), 199-211, Springer Verlag.

Because the estrogens present in men originate primarily from the peripheral aromatization of androgenic hormones (*Excerpta Medica*, 1979, 42 - 50, and *J. Clin. Endocrinol. Metab.* 27 (1967), 1103 - 1111), aromatase inhibitors are particularly suitable for lowering the estrogen level in men. Administration of aromatase inhibitors prevents or inhibits the formation of biologically active estrogens (estrogen biosynthesis). Per the invention, all aromatase inhibitors are suitable, which inhibit estrogen synthesis and themselves develop only a small amount of or no estrogens or other hormonal activity. Aromatase inhibitors per the present invention are, for example, testolactone (17a-oxa-D-homoandrosta-1,4-dien-3,17-dione, androst-4-ene-4-ol-3,7-dione (*Endocrinology* 100 (1977), 1684 - 1695), esters of androst-4-ene-4-ol-3,17-diones (US patent 4,235,893).

/6

Further suitable aromatase inhibitors are described, for example, in *Endocrinology* 92 (1973), 866 - 880, DE-OS 3,124,719 and US patent 4,289,762.

The invention also concerns agents for lowering the estrogen level for the prophylaxis and therapy of coronary heart diseases in men, in which case antiestrogens and, in particular, aromatase inhibitors are suitable for lowering the estrogen level.



The agents (estrogen-level reducers) can be processed into the usual application forms, for example, for oral, percutaneous or parenteral application, with the additives with the conventional additives of the galenical pharmacy, carrier substances and/or flavor correctors.

Utilizable for the preferred oral application are, in particular, tablets, dragées, capsules, pills, suspensions or solutions.

The medicines formulated, as indicated above, contain preferably

10 - 100 mg of tamoxifen, or biologically equivalent quantities of another antiestrogen, or

50 - 200 mg of testolactone, or biologically equivalent quantities of a different aromatase inhibitor.

In addition to that, it is also possible to administer antiestrogens or aromatase inhibitors together with  $\beta$ -receptor blockers for the treatment of heart diseases according to the present invention. Antiestrogens and  $\beta$ -receptor blockers or aromatase inhibitors or aromatase inhibitors and  $\beta$ -receptor blockers are preferably administered simultaneously in separate or combined dosage units. /7

$\beta$ -receptor blockers are applied together with antiestrogens or aromatase inhibitors in the same form and in a quantity equal or reduced by half relative to the treatment with  $\beta$ -blockers alone.

The weight ratio of aromatase inhibitors to  $\beta$ -blockers is approximately from 1:1 to 15:1 for testolactone as the aromatase inhibitor and propranolol as the  $\beta$ -blocker. The weight ratio of the combination can be appropriately adjusted according to the strength of the activity of the agents.

Also suitable for use as  $\beta$ -receptor blockers in addition to propranolol are all other known  $\beta$ -blockers, for example, oxprenolol, nadolol, pindolol, mepindolol, sotalol, etc.

Example 1

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100.0 mg 17 $\alpha$ -Oxa-D-homoandrosta-1,4-dien-3,17-dione  
(testolactone)

80.5 mg Lactose

39.5 mg Cornstarch

2.5 mg Polyvinyl-N-vinyl pyrrolidone 25

2.0 mg Aerosil

0.5 mg Magnesium stearate

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225.0 mg Total weight of the tablet, which is produced in a  
tableting press in the usual manner.

Example 2

50.0 mg 17a-Oxa-D-homoandrosta-1,4-dien-3,17-dione  
(testolactone)

115.5 mg Lactose

54.5 mg Cornstarch

2.5 mg Polyvinyl-N-vinyl pyrrolidone 25

2.0 mg Aerosil

0.5 mg Magnesium stearate

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225.0 mg Total weight of the tablet, which is produced in a  
tableting press in the usual manner.

Example 3

50.0 mg 17a-Oxa-D-homoandrosta-1,4-dien-3,17-dione  
(testolactone)

378.4 mg Castor oil

643.6 mg Benzyl benzoate

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1,072.0 mg ± 1 ml of solution

Example 4

50.0 mg (Z)-2-[p-(1,2-diphenyl-1-butenyl)-phenoxy]-N,N-  
dimethylethylamine (tamoxifen)

120.5 mg Lactose

59.5 mg Cornstarch

2.5 mg Polyvinyl-N-vinyl pyrrolidone 25

2.0 mg Aerosil

/9

0.5 mg Magnesium stearate

205.0 mg Total weight of the tablet, which is produced in a tableting press in the usual manner.

Patent claims

/10

- 1.) Agent for lowering the estrogen level for the prophylaxis and therapy of coronary heart diseases in men.
- 2.) Agent according to claim 1, on the basis of an antiestrogen, possibly in combination with a  $\beta$ -receptor blocker.
- 3.) Agent according to claim 1, on the basis of an aromatase inhibitor, possibly in combination with a  $\beta$ -receptor blocker.
- 4.) Agent according to claim 1, in an oral application form.
- 5.) Agent according to claim 1, for percutaneous or parenteral application.
- 6.) Agent according to claim 1, containing 10 - 100 mg of tamoxifen or biologically equivalent quantities of another antiestrogen.
- 7.) Agent according to claim 1, containing 50 - 200 mg of testolactone or biologically equivalent quantities of a different aromatase inhibitor.
- 8.) Prophylaxis and therapy of coronary heart diseases in men by lowering the estrogen concentration.
- 9.) Utilization of antiestrogens, possibly in combination with  $\beta$ -blockers, for the prophylaxis and therapy of coronary heart diseases according to claim 8.

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